2022 Buck Summer Scholar: Alexa Schlotter

My name is Alexa Schlotter, and I am a rising junior at Columbia University studying biomedical engineering and computer science. I am interested in a career at the intersection of the life sciences and technology, especially in relation to the biological aging process. This past year, I worked in the Miller Lab at the Columbia Irving Medical Center Mailman School of Public Health. At the Miller Lab, I focused on researching the transgenerational effects of environmental toxicants like pesticides on the development of neurodegenerative diseases. This summer at the Buck Institute, I have joined the Newman Lab. The Newman Lab focuses on investigating the role that ketone bodies play in promoting health and preventing Alzheimer's disease and decline in age-related memory. The long-term goal of the Newman Lab is to develop therapies that harness ketone bodies to increase the resilience of aging adults against age-related stresses and diseases. Ketone bodies are small metabolites that are synthesized primarily in the liver from fatty acids and are then exported for use as an energy source when the glucose level present is lower than what is energetically needed by the body.

My project this summer focuses on the NLRP3 inflammasome. The NLRP3 inflammasome is an immune receptor that is part of the innate immune system, the first line of defense against bacterial, viral, and fungal infections. The inflammasome is activated by a signal, which could include toxins from bacterial infections or double-stranded RNA from a viral infection.
When the NLRP3 inflammasome is activated, it secretes an inflammatory molecule called interleukin 1B (IL-1B). IL-1B can increases expression of genes for fever, pain, and hypotension, allowing for immune cells to infiltrate damaged tissue. This makes NLRP3 a key part of the immune system, protecting against a host of different infections. However, when the NLRP3 inflammasome is not properly regulated, it can lead to the development of a variety of inflammatory conditions, including Alzheimer's, diabetes, and various cancers. Therefore, the development of therapies combating these conditions has focused on inhibiting the NLRP3 inflammasome in different cell types.

Of interest in my project are microglia, a population of immune cells that are present in the central nervous system (CNS). Microglia are co-localized with amyloid-β plaques, deposits of amyloid-β protein in the brain that are a common hallmark of Alzheimer's disease (AD). This suggests that microglia may play a role in the early stages of the development of AD. In recent years, interest has risen in harnessing the effects of ketone bodies, particularly β-hydroxybutyrate (BHB), to develop therapies to combat Alzheimer's disease in the early stages. BHB levels are significantly lower in the blood of AD patients, indicating it is correlated with AD development.

Because of this possible connection, it is hypothesized that BHB may play a role in inhibiting the NLRP3 inflammasome in microglia, meaning it may be able to play a preventative role in Alzheimer's development. To test this hypothesis, I treated cells with varying concentrations of BHB and other ketone bodies and observed the secretion levels of IL-1B. Lowered concentrations of IL-1B would indicate that BHB is able to inhibit NLRP3-mediated secretion of IL-1B.

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